California Medicine
THE WESTERN JOURNAL OF MEDICINE

Editor
MALCOLM S. M. WATTS, M.D.

Associate Editor
LLOYD H. SMITH, JR., M.D.

Managing Editor
ROBERT F. EDWARDS
For information on preparation of manuscript, see advertising page 2

EDITORIAL

Disseminated Intravascular Coagulation: New Bottles For An Old Wine

SCARCELY A CLINICAL JOURNAL is published, nowadays, without an article or two ascribing some fresh disorder to inadvertent intravascular coagulation. The appealing view that many apparently diverse pathologic processes have a common basis in diffuse thrombosis within small blood vessels has a lusty champion in McKay, whose review appears elsewhere in this issue.

Like all new ideas, the concept that disseminated intravascular coagulation is an important pathologic process has its origins in the distant past. As early as 1834, de Blainville[1] demonstrated that the intravenous injection of brain tissue led immediately to lethal, massive intravascular clotting. A half century later, Woolridge[2] observed that animals would survive if the infusion of tissue extract was sufficiently slow; indeed, no gross intravascular clots could be found. For some time after the infusion, the animals' blood was incoagulable, and further infusions of tissue extracts were harmless. Mills[3] and others showed that the blood in such animals would not clot because it was depleted of fibrinogen. In modern terms, the tissues used in these various experiments furnished tissue thromboplastin which activated the extrinsic pathway of thrombin formation and, in this way, initiated clotting within the animals' blood stream. In agreement with this view, clotting factors other than fibrinogen have been found to be depleted (or "consumed") after the infusion of tissue extracts. Antihemophilic factor (Factor VIII),[4] proaccelerin (Factor V),[5] prothrombin (Factor II)[5] and platelets[6] disappear most rapidly, changes resembling those which take place when blood clots in a test tube. In addition, deficiencies of Christmas factor (Factor IX), Stuart factor (Factor X) and Factor VII may be detected.[7] At the same time, the plasma acquires inhibitory activity retarding the formation of a fibrin clot[8] and, inconstantly, fibrinolytic activity. Defibrination can also be brought about by the injection of thrombin[9] or certain snake venoms.[10]

In animals subjected to sublethal infusions of clot-promoting agents, few if any thrombi are found, even under the microscope. Two hypotheses have been proposed to explain this paradox. Perhaps the clots which form are promptly lysed by plasmin. This fibrinolytic enzyme is activated from its precursor, plasminogen, with particular facility if fibrin is present.[11] Were this true, the blood stream should contain degradation products of the digested fibrin. These products could readily account for the concomitant retarded formation of fibrin for, in the test tube, they inhibit the action of thrombin and interfere with the polymerization of fibrin.[12,13] Alternatively, the formation of fibrin initiated by the infusion of procoagulant substances might be incomplete. Conceivably, the first products of clotting, monomeric units of fibrin, perhaps polymerized with fibrinogen itself, might be readily removed from the blood stream before they had a chance to form macroscopic clots.[14,15] In support of this, material resembling fibrin has been found in reticuloendothelial cells after the infusion of clot-promoting agents. Of course, these hypotheses are not mutually exclusive, nor can one be certain that the fibrin ingested by macrophages has not already been lysed by plasmin.

Two clinical syndromes have been delineated

which seem to be the counterpart of these animal studies. In *amniotic fluid embolism,* amniotic fluid enters the maternal blood stream during parturition, as proved by the presence of fetal epithelial cells and hairs within the mother's blood vessels. In patients who survive the immediate effects of this disaster, a severe hemorrhagic tendency ensues, characterized by hypofibrinogenemia, thrombocytopenia, the appearance of thrombin-inhibitory and fibrinolytic activity in plasma, and other coagulative defects.[16] It is attractive to think that in this disorder the blood has been clotted within the maternal blood vessels by amniotic fluid or its contaminants. Similarly, *envenomation* by the bite of certain snakes may defibrinate the victim. When the venom is primarily a procoagulant, like that of the Malayan pit viper, the patient may survive the episode without difficulty, just as the patient with congenital afibrinogenemia will not bleed unless subjected to injury.[17] The benign results of this defibrination have suggested the use of snake venoms in the treatment of thrombotic states.[18]

In contrast to these two disorders, evidence that other pathologic processes are accompanied by intravascular coagulation rests upon indirect arguments varying in their cogency. Perhaps the clearest example is the hemorrhagic state which follows *massive transfusion of incompatible blood,* recalling to mind that one of the tissue extracts used in Woolridge's classic experiments was erythrocytic stroma. Under these conditions, hypofibrinogenemia and other clotting defects are often detectable.[19] Similarly, Schneider[20] attributed the defibrination which may complicate *premature separation of the placenta* to intravascular coagulation induced by the entrance of thromboplastic agents derived from decidua. Although alternative explanations of the hypofibrinogenemia seen in this condition have been offered, one can defibrinate an animal by the infusion of placental tissue.[21] On shakier grounds, the hypofibrinogenemia sometimes seen in patients with *carcinoma of the prostate,*[22] *leukemia*[23] or other *neoplasms* has been attributed to entrance into the blood stream of procoagulant substances derived from the tumor tissues. The same logic may account for the striking hypofibrinogenemia which may complicate severe sepsis. When afibrinogenemia was first detected in a case of *septic abortion,* this state was attributed to a failure of synthesis because coincidentally massive hepatic necrosis was present.[24] Subsequently, it became apparent that in this syndrome fibrinogen is consumed intravascularly through activation of the blood clotting mechanisms.[25] But this syndrome cannot yet be attributed to any bacterial product; perhaps the source of the procoagulant introduced into the patient's blood stream is her own damaged tissue. Similarly, severe hypofibrinogenemia and other clotting abnormalities have been discovered in some patients with *Waterhouse-Friderichsen syndrome,*[26] whether caused by the meningococcus or pneumococcus. Gross evidences of intravascular clotting are also to be found in *purpura fulminans,* a peculiarly unpleasant disease in which large patches of gangrene, usually superficial in nature, suddenly appear out of the blue, often some days after a streptococcal infection.[27] In this disorder, widespread vasculitis and thrombosis of small blood vessels can be demonstrated, suggesting once again that the procoagulant is derived from the patient's own damaged tissues.

Three advances led to the concept that still other pathologic states might induce widespread intravascular coagulation, perhaps insufficient in itself to cause significant hypofibrinogenemia but adequate to bring about ischemic damage. First, Merskey[28] and others demonstrated material immunologically like fibrin in the *serum* of persons who had apparently undergone intravascular coagulation. Presumably, this material either was fibrin which had been degraded by plasmin or was soluble, incompletely clotted fibrin. Were such "fibrin degradation products" to be found in other conditions, one might postulate that intravascular coagulation had taken place even though hypofibrinogenemia could not be detected. Second, Brain and his associates[29] showed that the red blood cells were severely damaged and took on a characteristic appearance as the result of experimental intravascular coagulation. The cells resembled those of *microangiopathic hemolytic anemia,* a state seen preeminently in *thrombotic thrombocytopenic purpura,* suggesting that in these states intravascular coagulation had occurred. Further, their experiments fortified the view that intravascular coagulation can be brought about by vascular damage, and that the hemolytic anemia which often accompanies such states may reflect physical damage to the erythrocytes as they are caught in the meshes of a fibrin clot. Here are the beginnings of an explanation for the syndrome of violent hemolytic anemia, thrombocyto-

penia and clotting abnormalities observed, for example, in some patients with *eclampsia.*[30] Finally, Little[31] found that he was able to halt the advance of purpura fulminans by the therapeutic administration of heparin, inferring that this disease was, as seemed apparent, the result of widespread intravascular coagulation. This observation has led to the belief that a favorable response to therapy with heparin is evidence that hypofibrinogenemia is due to intravascular coagulation. A striking example is the correction of hypofibrinogenemia which follows the use of heparin in women in whom there has been *intrauterine retention of a dead fetus.*[32] Although heparin has not always been helpful in disorders thought to be associated with intravascular clotting, its use is much more logical that that of epsilon aminocaproic acid, an agent which may compound the patient's difficulties by preventing lysis of thrombi.

Consideration of these three criteria has led to the view that disseminated intravascular coagulation plays an important part in such syndromes as *thrombotic thrombocytopenic purpura, renal cortical necrosis, malignant hypertension, cirrhosis of the liver, hyaline membrane disease, hemolytic-uremic syndrome* and *shock* due to a variety of mechanisms. McKay's review furnishes strong evidence in support of this hypothesis. We are only beginning to appreciate the role of more localized clotting in the *rejection of organ grafts.* And, turning cart before horse, Linton and his colleagues[33] now suggest that the *malignant phase of hypertensive disease* is secondary to renal changes brought about by the deposition of fibrin in renal vascular walls, a truly malignant sequel to intravascular coagulation. Perhaps, too, as Duguid[36] believes, Rokitansky's view that *atherosclerosis* is secondary to fibrin deposition in vascular endothelium is correct. We seem to have come a long way from de Blainville, yet we are only at the beginning of our understanding of the processes of intravascular coagulation and, as always, it is hard to see the future.

OSCAR D. RATNOFF, M.D.
Professor of Medicine, Case Western Reserve University School of Medicine

REFERENCES

1. de Blainville, H.M.D.: Injection de matiere cerebrale dans les veins, Gazette med. de Paris, p. 524, 1834.

2. Woolridge, L. C.: Über intravasculäre Gerinnungen, Arch. Anat. u. Physiol. (Physiol. Abt.), p. 397, 1886.

3. Mills, C. A.: The action of tissue extracts in coagulation of blood, J. Biol. Chem., 46:167, 1921.

4. Penick, G. D., Roberts, H. R., Webster, W. P., and Brinkhous, K. M.: Hemorrhagic states secondary to intravascular clotting. An experimental study of their evolution and prevention, AMA Arch. Path., 66:708, 1958.

5. Page, E. W., Fulton, L. D., and Glendening, M.B.: The cause of the blood coagulation defect following abruptio placentae, Amer. J. Obstet. Gynec., 61:1116, 1951.

6. Hartmann, R. C., Conley, C. L., and Krevans, J. R.: The effect of intravenous infusion of thromboplastin on "heparin tolerance," J. Clin. Invest., 30:948, 1951.

7. Rapaport, S. I., Hjort, P. F., Patch, M. J., and Jeremic, M.: Consumption of serum factors and prothrombin during intravascular clotting in rabbits, Scand. J. Haemat., 3:59, 1966.

8. Ratnoff, O. D., and Conley, C. L.: Studies on afibrinogenemia—II. The defibrinating effect of intravenous injection of thromboplastic material, Bull. Johns Hopkins Hosp., 88:414, 1951.

9. Mellanby, J.: Thrombase—Its preparation and properties, Proc. Roy. Soc. London, Series B, 113:93, 1933.

10. Mellanby, J.: The coagulation of blood—Part II—The action of snake venoms, peptone and leech extract, J. Physiol., 38:441, 1909.

11. Ratnoff, O. D.: Studies on a proteolytic enzyme in human plasma. IX. Fibrinogen and fibrin as substrates for the proteolytic enzyme of plasma, J. Clin. Invest., 32:473, 1953.

12. Niewiarowski, S., and Kowalski, E.: Un nouvel anticoagulant dérivé due fibrinogéne, Rev. Hemat., 13:320, 1958.

13. Bang, N. U., Fletcher, A. P., Alkjaersig, N., and Sherry, S.: Pathogenesis of the coagulation defect developing during pathological plasma proteolytic ("fibrinolytic") states—III. Demonstration of abnormal clot structure by electron microscopy, J. Clin. Invest., 41:935, 1962.

14. Lee, L., and McCluskey, R. T.: Immunohistological demonstration of the reticuloendothelial clearance of circulating fibrin aggregates, J. Exptl. Med., 116:611, 1962.

15. Shainoff, J. R., and Page, I. H.: Cofibrins and fibrin-intermediates as indicators of thrombin activity in vivo, Circul. Res., 8:1013, 1960.

16. Ratnoff, O. D., and Vosburgh, G. J.: Observations on the clotting defect in amniotic-fluid embolism, New Eng. J. Med., 247:970, 1952.

17. Reid, H. A., Chan, K. E., and Thean, P. C.: Prolonged coagulation defect (defibrination syndrome) in Malayan viper bite, Lancet, 1:621, 1963.

18. Bell, W. R., Pitney, W. R., and Goodwin, J. F.: Therapeutic defibrination in the treatment of thrombotic disease, Lancet, 1:490, 1968.

19. Conley, C. L.: Symposium on the use and misuse of blood transfusion in surgery: Untoward reactions from blood transfusion, Maryland State Med. J., 1:457, 1952.

20. Schneider, C. L.: "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of the end results during placenta abruptio, Surg. Gynec. Obstet., 92:27, 1951.

21. Copley, A. L.: Studies on human placental thromboplastin in vitro and in vivo, Science, 101:436, 1945.

22. Rapaport, S. I., and Chapman, C. C.: Coexistent hypercoagulability and acute hypofibrinogenemia in a patient with prostatic carcinoma, Am. J. Med., 27:144, 1959.

23. Rosenthal, R. L.: Acute promyelocytic leukemia associated with hypofibrinogenemia, Blood, 21:495, 1963.

24. Conley, C. L., Ratnoff, O. D., and Hartmann, R. C.: Studies on afibrinogenemia. I. Afibrinogenemia in a patient with septic abortion, acute yellow atrophy of the liver and bactermia due to E. coli, Bull. Johns Hopkins Hospital, 88:402, 1950.

25. Rubenberg, M. L., Baker, L. R. I., McBride, J. A., Sevitt, L. H., and Brain, M. C.: Intravascular coagulation in a case of Clostridium perfringens septicaemia: treatment by exchange transfusion and heparin, Brit. Med. J., 4:271, 1967.

26. Ratnoff, O. D., and Nebehay, W. G.: Multiple coagulative defects in a patient with Waterhouse-Friderichsen syndrome, Ann. Int. Med., 56:627, 1962.

27. Heal, F. C., and Kent, J.: Purpura fulminans with afibrinogenaemia, Canad. Med. Assoc. J., 69:367,1953.

28. Merskey, C., Kleiner, G. J. and Johnson, A. J.: Quantitative estimation of split products of fibrinogen in human serum, relation to diagnosis and treatment, Blood, 28:1, 1966.

29. Brain, M. C., Esterly, J. R., and Beck, E. A.: Intravascular haemolysis with experimentally produced vascular thrombi, Brit. J. Haemat., 13:868, 1967.

30. Pritchard, J. A., Weisman, R., Jr., Ratnoff, O. D., and Vosburgh, G. J.: Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy, New Eng. J. Med., 250:89, 1954.

31. Little, J. R.: Purpura fulminans treated successfully with anticoagulation—Report of a case, J. Amer. Med. Assoc., 169:36, 1959.

32. Sherman, E., and Middleton, E. B.: The management of missed abortion with hypofibrinogenemia, Maryland State Med. J., 7:300, 1958.

33. Linton, A. L., Gavras, H., Gleadle, R. I., Hutchison, H. E., Lawson, D. H., Lever, A. F., Macadam, R. F., McNicol, G. P., and Robertson, J. I. S.: Microangiopathic haemolytic anaemia and the pathogenesis of malignant hypertension, Lancet, 1:277, 1969.

34. Duguid, J. B.: Thrombosis as a factor in the pathogenesis of aortic atherosclerosis, J. Path. Bact., 60:57, 1948.